

REMARKS

The claims have been rejected under 35 U.S.C. §112. The claims have been amended to obviate the rejection.

Claims 1-2 and 8-21 have been rejected under 35 U.S.C. §112, second paragraph, as being unpatentable over Elango et al., U.S. 4,981,995 in view of Chaudhari et al., U.S. Patent No. 6,093,847.

The Examiner's rejection is respectfully traversed.

The Applicants' invention as claimed is directed to an improved process for the preparation of 2-aryl propionic acids. The process comprises the steps of reacting an aryl compound, an organic acid having essentially less than 6% water by volume and a palladium catalyst in an organic solvent at a temperature ranging from 30 to 130°C, for a period ranging between 0.3 to 4 hours, at pressures ranging between 50 to 1500 psig. The mixture is then cooled to an ambient temperature. Next, the reaction vessel is flushed with an inert gas and the solvent is removed by conventional methods. The catalyst is separated and the 2-aryl propionic acid is isolated.

Elango et. al. '995 is directed to a process wherein preparation of Ibuprofen from IBPE is carried out in a multiphase manner. More particularly, according to Elango et al., see Examples 4 and 9, during the process of preparing Ibuprofen an organic layer and an aqueous layer are formed which are thereafter separated.

According to the teachings of Elango et al., IBPE is reacted with CO in an acidic aqueous medium containing at least 10% of H₂O based on the weight of IBPE. Elango et al.

also teaches that dissociated hydrogen and chloride ions are essentially derived from hydrogen halide such as HCl/HBr (Please refer claims 4 and 5).

It is important to note that the presence of water in an amount in excess of 10% based on the weight of IBPE, simultaneously along with an acid such as HCl/HBr will only tend to form a bi-phasic system wherein the promoters and water form a separate aqueous phase and the catalyst & IBPE form an organic phase. In fact, the applicants would respectfully submit that the presence of water in an amount excess of 6% will tend to formation of bi-phasic system.

The present invention on the contrary teaches a process for preparation of 2-aryl propionic acid in a homogeneous phase. This is because the applicants have found that preparation of 2-aryl propionic acid in a homogeneous phase from the reactants is more beneficial in terms of percent selectivity and percentage conversion. The Applicants have noticed that percentage selectivity and percentage conversion are about 20% to 29% higher when 2-aryl propionic acids are prepared in a homogeneous phase as compared to a biphasic system.

To obtain a homogenous system, ideally the reaction should be carried out in a strictly anhydrous condition. However, as achieving strictly anhydrous condition is very difficult, the Applicants have determined that the amount of water should be less than 6%. If the amount of H₂O present exceeds 6%, a biphasic system is formed, eventually leading to a decrease of % selectivity and % conversion. The % selectivity in Elango et.al. does not teach beyond 74% when the same parameters are used as in the present process. In the present process, the selectivity is up to 99 %. Thus, the teaching of Elango et al. is directly in contradiction to the teachings of the present invention.

Choudhary et. al describe the process for the preparation of ibuprofen from 2-aryl alcohol using a very specific catalyst comprising a group VIII metal and semilabile chelating ligand containing a "N" donor and "O" group. The semilabile chelating agent imparts efficacy to the performance to that used in the process.

However, the applicants have once tried a different catalyst to arrive at a process wherein different type of palladium compounds can act like a catalyst. The Applicants do not claim that the palladium complex/compounds have not been known or used as catalysts earlier. However, the Applicants have achieved an improved process wherein different types of catalyst can be used interchangeably, thereby getting higher % selectivity, % conversion and production rate collectively.

The catalyst used by the applicants are very specific for a particular reaction and it can not be assumed that a catalyst that works in a particular reaction will work in another reaction or all catalyst will work in a particular reaction. Even minor modifications in a particular catalyst may change its suitability for a particular process. Due to its highly selective nature of catalyst, scientists have discovered that to a catalyst which can interchangeably be used in a reaction, say reaction A, may not work similarly in the interchangeable fashion in another reaction, say reaction B. To find out the suitability of a new catalyst in a specific reaction, the modifications in the catalyst are first carried out and then their suitability for a particular reaction is tested. Moreover, some time an unmodified catalyst may work perfectly in a reaction, whereas the same catalyst modified with a particular dopant may not work in the same reaction. Thus, in the present invention, the applicants modified the catalyst using different palladium complex and tested its suitability in the process for conversion of 2- Aryl propionic acid.

The applicants have made serious efforts for several years to conduct the experiments with various forms of palladium complex. In fact, they conducted a few hundred experiments with various embodiments of catalyst and other promoters. However, to their surprise they found excellent results.

Further, the inventor of the cited documents also realizes the significance of various aspects, which are critical for chemical process and just because of that they have conducted various experiments with various modification such that pressure, water content, acid used, additives catalyst, solvent etc. Examples; A to F in Elango et al. clearly indicate that due to presence/absence of dissociated hydrogen ion or halide ion in reaction environment effect the % conversion and % selectivity of ibuprofen i.e. it varies in the range of 33 to 99% and 0 to 78% respectively.

Similarly, a change of acid, i.e. from sulfuric acid to HBr acid, effect the % selectivity of ibuprofen from 42 -70 % to 59-85 % (Please refer to examples 11 to 17 of Elango et al.). Also, in various examples, changes of additive, solvent and reaction pressure effects the % conversion and % selectivity of the ibuprofen.

As indicated in examples 8 and 9 of Chaudhari et al. as the reaction pressure decreases, the production rate of ibuprofen reduces significantly i.e from 1190 hr^{-1} to 556 hr^{-1} . Whereas, in the present invention the production rate is 1450 hr^{-1} with up to 99% conversion and up to 98.5 % selectivity even at low pressure.

Whereas, the inventors of the present invention found higher production rate in the range of 1120 hr⁻¹ to 1450 hr⁻¹, conversion up to 99% and selectivity of ibuprofen up to 98.5% as compare to 25 hr⁻¹ to 1120 hr⁻¹ cited in the Chaudhary et al.

The present invention is also using a pressure of about 50 psig which was disclosed in previous citation in which the pressure range varying in the range of 50 to 1500 psig. However, the reference does not disclose or state that by reducing the pressure, better results can be obtained for the same end product. The range provided by the previous citation is very broad. In the present invention, an extremely low pressure is used, available in the range and getting the same end product, which was earlier, obtained at least 500 psig.

The cited art does not provide any reference to the lowering of the pressure and the corresponding optimal results. There is no disclosure or suggestion that makes the instant Application obvious.

The Applicants present process is capable of achieving the higher percentage conversion, percentage selectivity and high production rate by using the palladium complex catalyst, which was never tried or even suggested in the cited documents. These changes are not more sophistication of any existing process or combination of processes. Hence, it is not obvious to a person skilled in this art to use or even try the Applicants' process.

The chemical nature of the ligand incorporated in the catalyst used plays an important role in deciding the rate of reaction, reactivity of the catalyst, reaction conditions to be susceptible to oxidation of the substrate and other reactants used is minimized, resulting in a clearer and product with high purity and yield and there may be very less possibility of formation of undesirable byproduct. Otherwise it will also involves the unnecessary time consumption in auxiliary purification process for getting desired end product.

Applicants respectfully submit that the cited references also fail to provide the necessary motivation to a person who is skilled in this art by combining the cited references. It is axiomatic in Patent law that two or more references can not be combined to render obvious the claimed invention where there is no motivation in the references or elsewhere to make the asserted combination. In the present invention, there is no reason why one of ordinary skill in this art would have been motivated to combine the two citations to practice the claimed invention in view of the fact both the citations are distinct and complete on their own and there is no logical link neither identified nor involved between the documents to combine them. Also, it is well established that in order to combine any two documents, they should provide a reasonable expectation of success and such reasonably expected success was not achieved in combination of the documents as such. None of the prior art suggests that keeping the low pressure, low water content at a particular concentration or within a particular concentration ranges will lead to results. It is only after years of hard work and trial and error that the inventors have reached the present process values, which provides exceptionally good results. In addition, the applicants feel it is not proper to compare with the subject matter of the combined prior art for establishing the existence of obviousness. This hindsight approach is not an appropriate way to evaluate obviousness aspect of any invention. The Examiner has simply split the invention into various parts and has tried to link the points from wherever he could identify the prior art. A person skilled in the art is not motivated to read these two citations one after the other.

It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill

in the art. *Bausch & Lomb, Inc. v. Barnes-Hind, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986) Determination that novel combination would have been obvious requires supporting teaching in prior art, and retrospective view of inherency cannot serve as substitute for actual teaching or suggestion in prior art which supports selection and use of various elements in particular claimed combination. *In re Newell*, 13 USPQ2d 1248, (CAFC, 12,12,89) "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination.

In view of the foregoing, the Applicants contend that the amended claims and the claims dependent there from are in proper form. Applicants also respectfully contend that the teachings of Elango et al. '995 in view of Chaudhari et al. '847 do not establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Thus, claims 1, 2 and 8-21 are considered to be patently distinguishable over the prior art of record.

The application is now considered to be in condition for allowance, and an early indication of same is earnestly solicited.

Respectfully submitted,



Arlene J. Powers
Registration No. 35,985
Gauthier & Connors, LLP
225 Franklin Street, Suite 3300
Boston, Massachusetts 02110
Telephone: (617) 426-9180
Extension 110